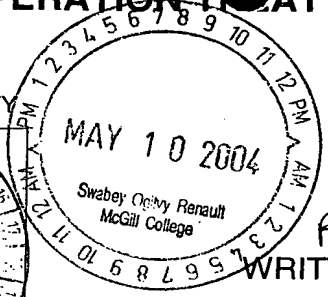
PATENT COOPERATION TREATY

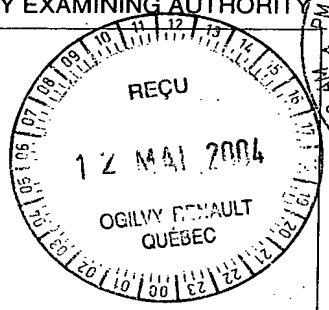
PCT/PTO 20 DEC 2004

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY



To: MG.

OGILVY RENAULT
Suite 1600
1981 McGill College Avenue
Montreal, Québec H3A 2Y3
CANADA



PCT

REPLY TO:
WRITTEN OPINION
(PCT Rule 66)

DUE ON AUG 04 2004

Date of mailing *(day/month/year)*	04.05.2004
Applicant's or agent's file reference ~~15890-IPCT~~ ? 6013-149PCT.	**REPLY DUE** **within 3 month(s)** from the above date of mailing

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/CA 03/00939	20.06.2003	05.07.2002

International Patent Classification (IPC) or both national classification and IPC
A61K45/00

Applicant
UNIVERSITE LAVAL et al.

1. This written opinion is the **first** drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

I	☒	Basis of the opinion
II	☐	Priority
III	☒	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
IV	☐	Lack of unity of invention
V	☒	Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
VI	☐	Certain documents cited
VII	☐	Certain defects in the international application
VIII	☐	Certain observations on the international application

3. The applicant is hereby **invited to reply** to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also: For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4 bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 05.11.2004

Name and mailing address of the international preliminary examining authority:

European Patent Office
D-80298 Munich
Tel. +49 89 2399 - 0 Tx: 523656 epmu d
Fax: +49 89 2399 - 4465

Authorized Officer
Böhmerova, E

Formalities officer (incl. extension of time limits)
Ladurner, Y
Telephone No. +49 89 2399-7913

I. Basis of the opinion

1. With regard to the **elements** of the international application *(Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed")*:

Description, Pages

1-35 as originally filed

Claims, Numbers

1-13 as originally filed

Drawings, Sheets

1/12-12/12 as originally filed

2. With regard to the **language**, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.

   These elements were available or furnished to this Authority in the following language: , which is:

   - ☐ the language of a translation furnished for the purposes of the international search (under Rule 23.1(b)).
   - ☐ the language of publication of the international application (under Rule 48.3(b)).
   - ☐ the language of a translation furnished for the purposes of international preliminary examination (under Rule 55.2 and/or 55.3).

3. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application, the international preliminary examination was carried out on the basis of the sequence listing:

   - ☐ contained in the international application in written form.
   - ☐ filed together with the international application in computer readable form.
   - ☐ furnished subsequently to this Authority in written form.
   - ☐ furnished subsequently to this Authority in computer readable form.
   - ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
   - ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. The amendments have resulted in the cancellation of:

   - ☐ the description, pages:
   - ☐ the claims, Nos.:
   - ☐ the drawings, sheets:

5. ☐ This opinion has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed (Rule 70.2(c)).

6. Additional observations, if necessary:

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been and will not be examined in respect of:

   ☐ the entire international application,

   ☒ claims Nos. 1-11

   because:

   ☒ the said international application, or the said claims Nos. 1-11 relate to the following subject matter which does not require an international preliminary examination (specify):

   see separate sheet

   ☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

   ☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

   ☐ no international search report has been established for the said claims Nos.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the Standard provided for in Annex C of the Administrative Instructions:

   ☐ the written form has not been furnished or does not comply with the Standard.

   ☐ the computer readable form has not been furnished or does not comply with the Standard.

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Claims	1,12,13
Inventive step (IS)	Claims	1,12,13
Industrial applicability (IA)	Claims	12,13

2. Citations and explanations

   see separate sheet

Re Item III

Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

Independent claim 1 relates to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(i) PCT).

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

Cited documents

Reference is made to the following documents:

D1: US-A-5 731 166 (GECZY CAROLYN ET AL) 24 March 1998

D2: US-A-6 103 497 (CORLEY NEIL C ET AL) 15 August 2000

D3: EP-A-0 263 072 (CIBA GEIGY AG) 6 April 1988

D4: DUNN C J ET AL: 'Increased expression of neutrophil MRP8 and MRP14 is associated with vascular adhesion molecule activation and differential leukocyte infiltration in delayed-type hypersensitivity suggesting a proinflammatory role for S100 calcium-binding proteins' DATABASE BIOSIS, Acc. No. PREV199799379823

D5: YEN TINA ET AL: 'Induction of the S100 chemotactic protein, CP-10, in murine microvascular endothelial cells by proinflammatory stimuli', BLOOD, vol. 90, no. 12, 15 December 1997, pages 4812-4821

D6: LAGASSE E ET AL: 'MOUSE MRP8 AND MRP14, TWO INTRACELLULAR CALCIUM-BINDING PROTEINS ASSOCIATED WITH THE DEVELOPMENT OF THE MYELOID LINEAGE', BLOOD, vol. 79, 1992, pages 1907-1915

D7: LACKMANN M: 'IDENTIFICATION OF A CHEMOTACTIC DOMAIN OF THE PRO-INFLAMMATORY S100 PROTEIN CP-10' JOURNAL OF IMMUNOLOGY, vol. 150, no. 7, 1 April 1993, pages 2981-2991

D8: DEVERY JANNINE M ET AL: 'Acute inflammatory activity of the S100 protein CP-10: Activation of neutrophils in vivo and in vitro.' JOURNAL OF IMMUNOLOGY,

vol. 152, no. 4, 1994, pages 1888-1897

D9: ROULEAU PASCAL ET AL: 'The calcium-binding protein S100A12 induces neutrophil adhesion, migration, and release from bone marrow in mouse at concentrations similar to those found in human inflammatory arthritis.' CLINICAL IMMUNOLOGY, vol. 107, no. 1, 20 April 2003, pages 46-54

Unless indicated otherwise reference is made to the passages considered relevant in the search report.

Novelty

Subject-matter of independent claims 1, 12, 13 is considered to lack novelty under Art. 33(1) and (2) PCT for the following reasons:

Present claims 1 and 13 are directed to a method for systemic modulation of an inflammatory reaction in an individual comprising administering a chemotactic factor inhibitor selected from the group consisting of an S100 protein, a protein of MRP family, calprotectin and calgranulin and the analogical second medical use. Claim 12 is directed to a composition for modulating an inflammatory reaction comprising a chemotactic factor inhibitor selected from the group consisting of an S100 protein, a protein of MRP family, calprotectin and calgranulin.

D1 discloses CP-10 polypeptide, a pharmaceutical composition comprising such polypeptide and a method for modulating an inflammatory response in a mammal comprising the step of administering CP-10 protein. CP-10 is murine S100A8 (see D9). D1 further teaches the use of monoclonal antibodies against CP-10 or non-functional analogues or antagonist of CP-10 for inhibition of inflammation in the treatment of conditions such as rheumatoid arthritis, systemic lupus erythematosus, coeliac disease, multiple sclerosis, rejecting grafts, tumors etc..

D2 discloses S100P proteins S100P1 and S100P2, pharmaceutical compositions comprising S100P1 or S100P2 (column 3, lines 14-17, column 4, lines 19-22) and the use of these compositions for the diagnosis, prevention or treatment of neuronal, vesicle trafficking, immunological and neoplastic disorders (column 11, lines 1-7). D2 further teaches the use of antagonists or antibodies against S100P protein in the

treatment or prevention of diseases including inflammatory bowel disease, rheumatoid arthritis, osteoarthritis, leukemia etc..

The above disclosure of D1 and D2 anticipates novelty of present claims 1, 12 and 13.

Inventiveness

As the subject-matter of claims 1, 12, 13 is considered as lacking novelty, no inventiveness can be acknowledged at this stage.

In case novelty of present claims 1, 12 and 13 is acknowledged, the subject-matter of those claims would be considered as lacking an inventive step under Article 33(1) and (3) PCT for the following reasons:

The problem to be solved by the application can be defined as to provide a medicament for modulation of inflammatory reaction. Solution proposed by the application is an inhibitor of a chemotactic factor selected from S100 protein, a protein of MRP family, calprotectin or calgranulin. The application does not comprise experimental data directly proving such an effect of chemotactic factor inhibitors. The data present in the application prove the following facts:
- injection of LPS into air pouch (model of inflammation) causes accumulation of leukocytes, release of S100A8, S100A9 and S100A8/A9 in the place of injection and increase of circulating neutrophils and S100A9 and S100A8/A9 levels;
- these effects are inhibited by anti-S100A8 or anti-S100A9 antibodies;
- intravenous injection of S100A8 or S100A9 causes serum neutrophilia and release of bone marrow neutrophils into blood.

However, all the above effects are known from the prior art - see documents D3-D8.
D3 teaches that serum levels of MRP-8 and/or MRP-14 are elevated in inflammatory conditions.
D4 teaches that infiltrating neutrophils express and release MRP8 and MRP14. This may represent an important systemic and local mechanism for recruitment of neutrophils and monocytes into the delayed type hypersensitivity inflammatory site through bone marrow mobilization and chemotaxis of neutrophils and monocytes.
D5 teaches that CP-10 (murine S100A8) is expressed in neutrophils, LPS-activated

macrophages and LPS-activated murine endothelioma cell lines.
D6 discloses that MRP8 and MRP14 are highly expressed in recruited neutrophils and monocytes in thoglycollate-induced peritoneal inflammatory exudates.
D7 teaches that intradermal injection of native CP-10 elicited sustained recruitment of neutrophils and mononuclear cells over 24 hours in rats. Sustained cellular recruitment is typical for a delayed type hypersensitivity responses.
D8 teaches that CP-10 has a potent chemotactic activity for murine and human myeloid cells. An i.p. injection of CP-10 induced infiltration of neutrophils in mice. LPS injection to murine footpads induced inflammation and secretion of CP-10.

If the experimental data provided by the application should be considered to be sufficient to prove that the claimed solution actually solves the technical problem, this solution must be directly derivable from those data without any further inventive activity. If this applies, the same conclusion must apply to the analogical data known from the prior art (D3-D8). Therefore, those data should be considered as being sufficient to lead a skilled person to the claimed solution without involvement of an inventive activity. Consequently, the solution as claimed is to be considered as being obvious based on the data known from D3-D8.

Industrial applicability

Subject-matter of independent claims 12, 13 is considered to be industrially applicable under Art. 33(1) and (4) PCT.

For the assessment of the independent claim 1 on the question whether it is industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.